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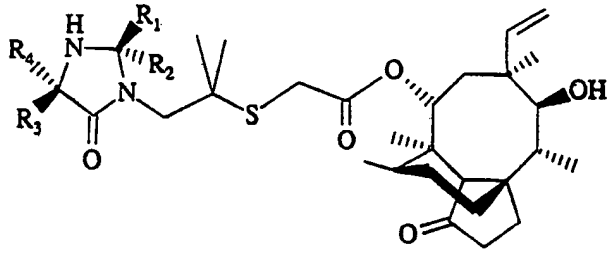
(54) Title: PLEUROMUTILIN DERIVATIVES



(I)

(57) Abstract

A compound of formula (I), in which each of R_1 and R_2 is independently hydrogen, alkyl or, together with the carbon atom to which it is bonded, a cycloalkyl; and each of R_3 and R_4 is independently hydrogen, alkyl or substituted alkyl. The compounds are useful intermediates and prodrugs.

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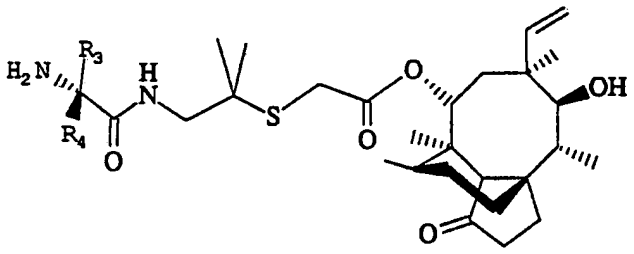
Pleuromutilin Derivatives

This invention concerns pleuromutilin derivatives that are useful as stable pro-pleuromutilin antibacterial agents and that are useful in the production of pleuromutilin antibacterial agents.

Pleuromutilin compounds of the formula II

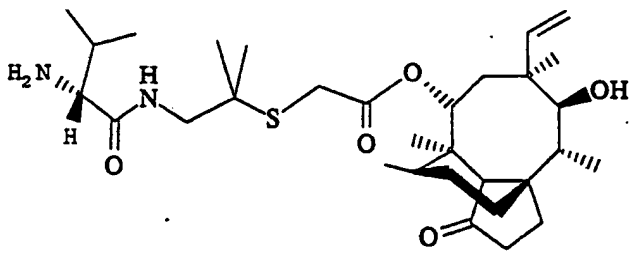


II

in which each of R_3 and R_4 is independently hydrogen, alkyl or substituted alkyl, are disclosed in European patent application EP 0 153 277. These compounds have useful biological properties; especially chemotherapeutic properties. For example the compounds of the formula II inhibit the growth of bacteria, Mycoplasms and Chlamydia and have antiparasitic properties (particularly against coccidia) and growth promoting activity. Hence these compounds can be used as medicaments and animal feeds.

However the compounds of the formula II could not previously be obtained in highly purified form since they are not available in crystalline form. As disclosed in EP 0 153 277, they could only be purified using chromatographic techniques.

Austrian Patent 392 272 discloses methods for the extraction and purification of compounds of the formula IV

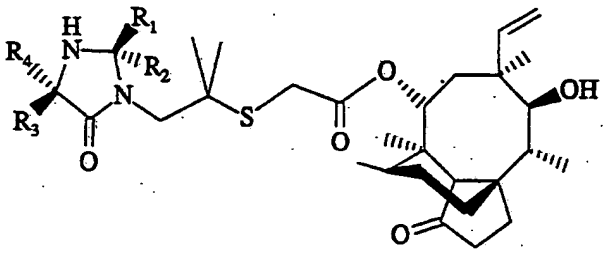


IV

using specific solvents but analogous compounds with similar separation coefficients are not separated off and highly pure forms cannot be obtained.

Therefore there is a need for a route for preparing compounds of formula II that enables the compounds to be obtained in highly purified form (for example in crystalline form). There is also a need for stable compounds which may be used as pro-drugs for the compound of formula II.

Accordingly, in one aspect this invention provides compounds of the formula I



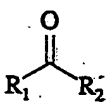
I

in which each of R_1 and R_2 is independently hydrogen, alkyl or, together with the carbon atom to which it is bonded, a cycloalkyl group; and each of R_3 and R_4 is independently hydrogen, alkyl or substituted alkyl. The compounds of the formula I are easily isolated in crystal form and hence are easily purified. Therefore the compounds of the formula I are useful intermediates in the production of compounds of the formula II in that they enable the preparation and isolation of highly purified forms of the compounds of formula II.

Preferably each R_1 and R_2 is independently H or C_1 to C_6 alkyl, or forms, together with the carbon atom to which it is bonded, a cycloalkyl ring of up to 6 carbon atoms (for example a 5 membered ring).

Preferably each R_3 and R_4 is independently H or C_1 to C_6 alkyl.

The invention also provides a process for the production of the compounds of the formula I comprising reacting a compound of formula II as defined above with a carbonyl compound of the formula III



III

in which R_3 and R_4 are as defined above, and isolating the compound of the formula I in free base or acid addition salt form. The compound of formula I may be obtained in crystalline form.

The reaction may be carried out in a suitable solvent such as a lower alcohol (for example methanol, ethanol or isopropanol).

The carbonyl compound of the formula III is preferably acetone, butan-2-one or cyclopentanone.

The invention also provides a method of producing compounds of the formula II as defined above in highly purified form (for example above 95% pure) comprising heating a compound of the formula I in the presence of an acid or a solvent, or both, and isolating the compound of the formula II in free base or acid addition salt form. Therefore, to produce compounds of the formula II in pure form, these compounds may be produced as conventionally produced to provide them in impure form. They may then be reacted with a carbonyl group of formula III as described above to provide the compounds of the formula I which may be readily purified since they are obtainable in crystalline form. The compounds of the formula I may then be converted to compounds of the formula II as described above.

Preferably the acid is a weak solution of hydrochloric acid or is a mixture of a solvent and a weak solution of hydrochloric acid.

The invention also provides the use of a compound of formula I as defined above in the preparation of compounds of the formula II in highly purified form.

The invention also provides a compound of the formula II in highly purified form (for example at least 95% and more preferably at least 98% pure).

The compounds of the formula I are extremely useful intermediates that enable the preparation of compounds of the formula II in highly purified form. However the compounds of the formula I are also useful as stable pro-drug forms of the compounds of the formula II because, at physiological pH's, they are released more slowly and in lower local concentrations. Also, they have lower basicity than the compounds of formula II and hence have better shelf-life.

Therefore the invention also provides a pharmaceutical composition comprising a compound of the formula I, as defined above, and a pharmaceutically acceptable carrier. Preferably the composition is in a form suitable for parenteral administration; for example

as an injectable solution. Since the compounds of the formula I are hydrolysed slowly under physiological conditions and are released slowly, the pharmaceutical compositions act as retard forms of compositions that contain compounds of the formula II.

The compounds of the formula I may also be used as a stable form of the compounds of formula II in animal feeds. The imidazolidine moiety of the compounds of formula I is more stable against enzymatic hydrolysation than the corresponding moiety of the compounds of formula II. Hence feeds which contain the compounds of formula I are more resistant to decomposition caused by enzymes commonly found in animal feeds.

In use the effective dosage will vary depending upon the particular compound employed, the mode of administration, and the treatment desired. However satisfactory results as anti-bacterials and anti-anaerobics can be obtained when the compounds are administered at a daily dosages similar to those described for compounds of the formula II in EP 0 153 277. If the compound is administered internally, the dosage form may contain the compound of formula I in admixture with a solid or liquid carrier or diluent.

For the prophylaxis of microorganism infections and for growth promotion in domestic animals, the dosage will vary depending upon the size and age of the animal and the effect desired. For example, for prophylactic treatment relatively low doses may be administered over a long time. Preferred doses in drinking water and foodstuffs are similar to those described for compounds of the formula II in EP 0 153 277. For pigs, it is preferred to administered the compound in foodstuffs. In this form, the compounds of the formula I are useful in the prophylactic treatment of swine dysentery.

Examples of the invention are now described, by way of example only. All temperatures are given in degrees centigrade.

Example 1 14-O-{[1-(2,2-Dimethyl-5(R)-isopropyl-imidazolidin-4-on-3-yl)-2-methyl-propan-2-yl]thioacetyl}mutilin

100 g of 14-O-{1-[(D)-2-amino-3-methylbutyrylamino]-2-methylpropan-2-yl-thioacetyl}mutilin hydrochloride are dissolved in 1000 ml water. 1000 ml tert.butylmethylether are added and the pH is adjusted to about 9 by the addition of 10 N sodium hydroxide. The phases are then separated and the organic phase is washed twice with about 200 ml water. The tert.butylmethylether is distilled off and the residue is

dissolved in ethanol. The ethanol is evaporated off and the residue collected. The residue is dissolved in 750 ml ethanol and 250 ml acetone and the mixture refluxed for 5 hours. Thereafter the mixture is left at room temperature for about 40 hours before being subjected to evaporation at 30 °C and under weak vacuum (about 120 m bar). About 650 ml of the ethanol/acetone solvent is evaporated off. The remaining crystal suspension is cooled with ice and stirred for an hour. The crystals are filtered, washed with cold ethanol and dried in a vacuum drier. The filtrate obtained from the filtration step is evaporated and the residue dissolved in 75 ml ethanol and 25 ml acetone. The mixture is left to stand for 48 hours at room temperature and the precipitate, in the form of crystals, then filtered off. The crystals are then washed with cold ethanol and dried in a vacuum drier. The dried crystals melt at a temperature of about 174 to 177 °C.

Example 2 14-O-{[1-(2,2-Dimethyl-5(R)-isopropyl-imidazolidin-4-on-3-yl)-2-methyl-propan-2-yl]thioacetyl}mutilin

100 g of 14-O-{1-[(D)-2-amino-3-methylbutyrylamino]-2-methylpropan-2-yl-thioacetyl}mutilin hydrochloride are dissolved in 1000 ml water. 1000 ml tert.butylmethylether are added and the pH is adjusted to about 9 to 10 by the addition of 10 N sodium hydroxide. The phases are then separated and the organic phase is washed twice with about 200 ml water. The tert.butylmethylether is distilled off and the residue is dissolved in 200 ml acetone. The acetone is evaporated off and the residue collected. The residue is dissolved in 1000 ml acetone, 50 g of a 0.3 nm molecular sieve (obtained from Merck) is added and the mixture is refluxed for 27 hours. Thereafter the mixture is left at room temperature overnight. 3 g of activated charcoal is then added, the mixture is stirred for 5 minutes and is then filtered. The filtrate is evaporated at normal pressures to a volume of about 200 ml. Seeding crystals are then added to the clear solution and the solution stirred for an hour at room temperature and 2 hours in an ice bath. The precipitation is filtered off, washed with tert.butylmethylether and dried in a vacuum drier. The dried crystals melt at a temperature of about 174 to 177 °C.

Example 3 14-O-{[1-(2,2-Dimethyl-5(R)-isopropyl-imidazolidin-4-on-3-yl)-2-methyl-propan-2-yl]thioacetyl}mutilin

150 g of 14-O-{1-[(D)-2-amino-3-methylbutyrylamino]-2-methylpropan-2-yl-thioacetyl}mutilin hydrochloride are dissolved in 1500 ml water and the mixture stirred. 800 ml tert.butylmethylether are added and the pH is adjusted to about 9 by the addition of 10 N sodium hydroxide. The phases are then separated and the organic phase is washed twice with about 500 ml water. 650 ml the tert.butylmethylether is evaporated off under normal pressure at temperature of 60°. The residue is dissolved in 186 ml acetone and 564 ml methanol and the mixture refluxed for 5 hours. Thereafter the mixture is left at room temperature for about 67 hours before being subjected to evaporation at 30 °C under vacuum. 450 ml isopropanol is added and the mixture stirred at room temperature for about 4 hours. The crystal suspension is cooled to about 0° and left over night. The crystals are filtered, washed with isopropanol and tert.butylmethylether, and dried in a vacuum drier. The dried crystals melt at a temperature of about 174 to 177 °C.

Example 4 14-O-{[1-(2,2-Dimethyl-5(R)-isopropyl-imidazolidin-4-on-3-yl)-2-methyl-propan-2-yl]thioacetyl}mutilin

The procedure set out in example 3 is followed except that the evaporation residue is dissolved in 480 ml methanol and 120 ml tert.butylmethylether instead of isopropanol. The dried crystals obtained melt at a temperature of about 174 to 177 °C.

Example 5 14-O-{[1-(2,2-Dimethyl-5(R)-isopropyl-imidazolidin-4-on-3-yl)-2-methyl-propan-2-yl]thioacetyl}mutilin

1 g of 14-O-{1-[(L)-2-amino-3-methylbutyrylamino]-2-methylpropan-2-yl-thioacetyl}mutilin hydrochloride is dissolved in 10 ml water. 10 ml tert.butylmethylether are added and the pH is adjusted to about 9 to 10 by the addition of 10 N sodium hydroxide to provide the compound in free base form. The phases are then separated and the organic phase is washed twice with water. The tert.butylmethylether is distilled off and the residue is dissolved in acetone. The acetone is evaporated off and the residue

collected. The residue is dissolved in 10 ml acetone, 1 g of a 0.3 nm molecular sieve is added and the mixture is refluxed for 48 hours. Thereafter the mixture is filtered. The filtrate is evaporated in a rotary evaporator and the residue collected. The residue is dissolved in 2 ml acetone and seeding crystals are then added. After 2 hours at room temperature, the precipitation is filtered off, washed with tert.butylmethylether and dried in a vacuum drier. The dried crystals melt at a temperature of about 170 to 173 °C.

Example 6 14-O-{[1-(2-ethyl-5(R)-isopropyl-2-methyl-imidazolidin-4-on-3-yl)-2-methyl-propan-2-yl]thioacetyl}mutilin

A procedure analogous to that set out in example 2 is followed except that the evaporation residue is dissolved in methanol and, instead of acetone, 2-butanone is used. The dried crystals melt at a temperature of about 156 to 158 °C.

Example 7 14-O-{[1-(5(R)-isopropyl-2,2-tetramethylene-imidazolidin-4-on-3-yl)-2-methyl-propan-2-yl]thioacetyl}mutilin

A procedure analogous to that set out in example 6 is followed except that, instead of 2-butanone, cyclopentanone is used. The dried crystals melt at a temperature of about 130 to 132 °C.

Example 8 14-O-{1-[(D)-2-amino-3-methylbutyrylamino]-2-methylpropan-2-yl-thioacetyl}mutilin hydrochloride

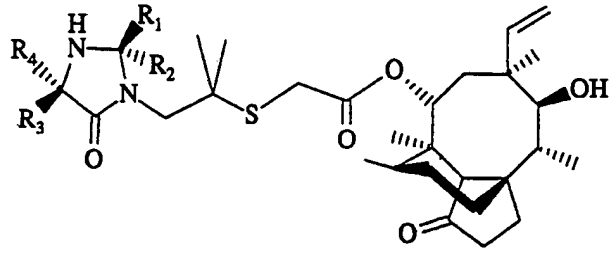
20 g of 14-O-{[1-(2,2-Dimethyl-5(R)-isopropyl-imidazolidin-4-on-3-yl)-2-methyl-propan-2-yl]thioacetyl}mutilin is dissolved in 80 ml water and 2.9 ml of 37% hydrochloric acid are added. The mixture is warmed to 90° for an hour. The clear solution is lyophilized or spray dried to provide the title compound in pure form (98% purity).

Example 9 14-O-{1-[(D)-2-amino-3-methylbutyrylamino]-2-methylpropan-2-yl-thioacetyl}mutilin hydrochloride

10 g of 14-O-{[1-(2,2-Dimethyl-5(R)-isopropyl-imidazolidin-4-on-3-yl)-2-methyl-propan-2-yl]thioacetyl}mutilin is dissolved in 100 ml methanol and 9.3 ml of 2N hydrochloric acid are added. The mixture is refluxed for about 1.5 hours and then dried in a rotary evaporator. The residue is dissolved in 50 ml water and the solution is lyophilized to provide the title compound in pure form (98% purity).

Claims:

1. A compound of the formula I



I

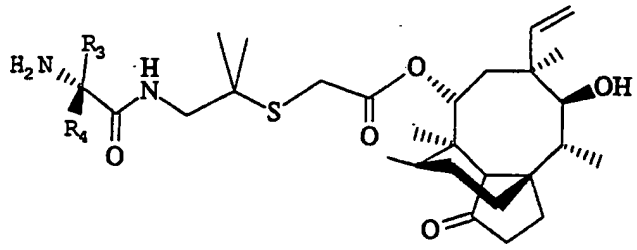
in which each of R_1 and R_2 is independently hydrogen, alkyl or, together with the carbon atom to which it is bonded, a cycloalkyl; and each of R_3 and R_4 is independently hydrogen, alkyl or substituted alkyl.

2. A compound according to claim 1 in which R_1 and R_2 are methyl.

3. A compound according to claim 1 which is 14-O-{[1-(2,2-Dimethyl-5(R)-isopropyl-imidazolidin-4-on-3-yl)-2-methyl-propan-2-yl]thioacetyl}mutilin.

4. A compound of the formula I according to claim 1 in crystalline form.

5. The use of compounds of the formula I, as defined in claim 1, in the production of compounds of the formula II

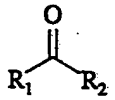


II

in which R_3 and R_4 are as defined in claim 1, in highly purified form.

6. A process for the production of compounds of the formula II, as defined in claim 5, in highly purified form comprising heating a compound of the formula I, as defined in claim 1, in the presence of an acid or a solvent, or both, and isolating the compound of the formula II in free base or acid addition salt form.

7. A process for the production of compounds of the formula I, as defined in claim 1, comprising reacting a compound of formula II, as defined in claim 5, with a carbonyl compound of the formula III



III

in which R_3 and R_4 are as defined above, and isolating the compound of the formula I in free base or acid addition salt form.

8. A process according to claim 7 which is carried out in a solvent selected from methanol, ethanol and isopropanol, or mixtures thereof.

9. In a process for the production of compounds of the formula II, as defined in claim 5, in free base or acid addition salt form, wherein the improvement comprises converting the compounds of the formula II into compounds of formula I by reacting with a carbonyl group of formula III as defined in claim 7; purifying the compounds of the formula I; and converting the purified compounds of formula I into the compounds of formula II by heating in the presence of an acid or a solvent, or both, and isolating the compound of the formula II in free base or acid addition salt form.

10. A compound of the formula II as defined in claim 5 in highly purified form.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/01033

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D233/32; C07C323/52; A61K31/415; A61K31/22

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; C07C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 421 364 (BIOCHEMIE G.M.B.H.; AUSTRIA (AT)) 10 April 1991 cited in the application see the whole document	1-10
Y	* Compounds of formula I * ---	5-9
A	EP,A,0 153 277 (SANDOZ A.-G.; SWITZ. (CH)) 28 August 1985 cited in the application see the whole document	1-10
Y	* compounds of formula I * ---	5-9
Y	EP,A,0 013 768 (SANDOZ AG) 6 August 1980 see the whole document ---	5-9

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
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International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Bernd Kissler

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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Y	TETRAHEDRON, (INCL. TETRAHEDRON REPORTS) vol. 44, no. 17, 1988, OXFORD GB pages 5277 - 5292 FITZI, ROBERT; SEEBACH, DIETER : 'Resolution and use in .alpha.- amino acid synthesis of imidazolidinone glycine derivatives.' * see scheme 2 and examples of the hydrolysis of 4-imidazolidinones to amino acids on page 5289 *	5-9
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Y	JOURNAL OF MEDICINAL CHEMISTRY. vol. 19, no. 1, 1976, WASHINGTON US pages 161 - 163 SMISSMAN, EDWARD E.; INLOES, ROGER L.; EL-ANTABLY, SAMIR; SHAFFER, PHYLLIS J. 'Specificity in enzyme inhibition. 3. Synthesis of 5-substituted-2,2-dimethyl-4-imidazolidinones as inhibitors of tyrosine decarboxylase and histidine decarboxylase' see the whole document	5-9

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9301033
SA 73408

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